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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/986,568	12/05/97	BACH J	040388/0110

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EXAMINER	
VANDERVEGT, F	
ART UNIT	**PAPER NUMBER**
1644	6

DATE MAILED: 06/24/98

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/986,568	Bach et al
Examiner	**Group Art Unit**
F. Pierre VanderVegt	1644

☒ Responsive to communication(s) filed on *Dec 5, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* ~~is~~/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15* ~~is~~/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, *substitute* PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3 & 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, *substitute* PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-15 are currently pending in this application.

Claim Objections

1. Claims 2 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The "non mitogenic anti-CD3 active principle" recited in lines 1-2 of claim 2 is already "a non mitogenic anti-CD3" as recited to conclude the claim. Applicant is merely repeating the property. Applicant is apparently attempting to add the limitation that said "non mitogenic anti-CD3 active principle" is an "non mitogenic anti-CD3 antibody." Appropriate corrections should be made.

The recitation "$F(ab')_2$ fragment is such as obtained by pepsin digestion" in claim 8 adds no further limitation to the base claim because it is an inherent property of $F(ab')_2$ fragments in general.

Claim Rejections - 35 U.S.C. § 112

2. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

While Applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "principle" in claims 1-6 and 13-15 is used by the claim to mean "compound," while the accepted meaning is "a basic truth, a rule or standard, a moral standard, a policy, a basic quality, a law or a basic source."

Claim 3 recites the limitation "antibody" in line 1. There is no antecedent basis for this limitation in the claim. Base claim 1 recites only "anti-CD3 active principles." Applicant is apparently attempting to further limit the antibody, as set forth in paragraph 1 supra, and

Claim 5 is ambiguous and unclear in its recitation of "$F(ab)_2$" in line 3, a species of antibody fragment which is non-existent. Said recitation must be replaced by either --F(ab)-- or --$F(ab')_2$--.

Claim 10 is improper in its recitation of "rheumatoïd" in line 2. Said recitation should be replaced by the American English spelling --rheumatoid--.

Claims 14 and 15 are ambiguous and unclear in their recitation of "unit dose" in line 3. There is no indication as to what the "unit" is defined as in the claim. The term could relate to units as being a fixed volume or weight, a per-subject administration or to a dosage dependent or to a dosage per pound or kilogram of the subject's body weight, for example.

Claim Rejections - 35 U.S.C. § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-5, 8, 9 and 13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chatenoud et al (A5 on form PTO-1449), as evidenced by Hughes et al (A4).

The Chatenoud et al reference teaches the induction of antigen-specific unresponsiveness in NOD mice with full-blown disease (Abstract in particular), by injection of non-mitogenic anti-CD3 monoclonal antibody (mAb) $F(ab')_2$ fragments (page 123, subsection "Mice and Antibodies in particular), resulting in complete remission of overt disease (Abstract in particular). Although it is not specifically stated by Chatenoud et al, it is a fact well known in the art that $F(ab')_2$ fragments are non mitogenic because they do not induce the release of cytokines like intact mAbs do, as evidenced by Hughes et al's teachings using the same hamster monoclonal antibody, 2C11,

for treatment in an unrelated autoimmune disease model (page 324, column 2 in particular). Chatenoud et al also teaches that the production of the anti-CD3 monoclonal antibody $F(ab')_2$ fragments is by "conventional pepsin digestion of the entire antibody molecule" (page 123, subsection "Mice and Antibodies in particular). The prior art teaching clearly anticipates the claimed invention.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Racadot et al (U on form PTO-892) in view of Güssow et al (V) and Chatenoud et al (A5).

Chatenoud et al has been discussed supra. Chatenoud et al does not teach murine mAbs, humanized mAbs or the treatment of multiple sclerosis. Racadot et al teaches the treatment of multiple sclerosis in human patients with a dosage of 5 mg/day of a murine monoclonal antibody designated muromonab-CD3, a.k.a. OKT-3 (page 201, subsection 1.2.3 in particular). Racadot et al also teaches that the treatment is associated with a dramatic decrease in T cell count and the induction of clonal anergy (page 202, first new paragraph in column 2 in particular). However, Racadot et al teaches a drawback in the treatment in that all patients developed anti-murine Abs and some patients deteriorated during therapy (page 201, subsection 1.2.3 in particular) and a

massive cytokine release (page 203, section 3 in particular). The skilled artisan would have readily recognized that the massive cytokine release associated with muromonab-CD3 treatment could be averted through the use of $F(ab')_2$ fragments of the mAb as taught by Chatenoud et al. The skilled artisan would have further recognized this still leaves the obstacle of the generation of anti-murine Abs in the patient because Güssow et al teaches that anti-murine Abs are still generated to the murine framework regions which remain in murine-human chimeric Abs (pages 99-100 in particular), which are essentially murine $F(ab')_2$ fragments fused to a human Fc region. Güssow et al teaches that this problem can be overcome by reshaping, humanization, of the murine Ab. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the effective muromonab-CD3 mAb by humanization as taught by Güssow et al in order to alleviate the anti-murine complications taught by Racadot et al. One would have been further motivated to modify the humanized muromonab-CD3, by pepsin digestion of the entire humanized antibody to generate F(ab')2 fragments to use for treatment as taught by Chatenoud et al in order to eliminate the massive cytokine release associated with treatment using intact anti-CD3 antibodies. One would have been motivated to combine these references with a reasonable expectation of success by the teachings of Racadot et al and Chatenoud et al that anti-CD3 treatment induces tolerance in an ongoing autoimmune reaction and by the teachings of Chatenoud et al and Güssow et al which address the problems taught to be associated with intact muromonab-CD3 treatment by Racadot et al. Claim 6 is included because highly purified, endotoxin free reagents are routinely prepared in the art and are a well-known requirement for treatment of human patients. Claims 10 and 11 are included because, while none of the cited references specifically teach the treatment of rheumatoid arthritis or psoriasis, the anti-CD3 course of treatment does not require the administration of disease specific antigens or agents to the subject, nor is there a requirement of knowledge of the target antigen in the disease. Therefore, the skilled artisan would be able to reasonably predict that the method would be useful for the treatment of any autoimmune condition in which the involvement of T lymphocytes is a major factor in the etiology of the disease.

Conclusion

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. The Group and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

8. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The examiner can normally be reached Monday through Friday from 8:00 am to 4:30 pm ET. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

June 23, 1998
F. Pierre VanderVegt, Ph.D.
Patent Examiner
Art Unit 1644

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT 182